A second test, which has been used to assess the effects of smoking on sensation, is the critical flicker fusion test. Briefly, this task requires the subject to discriminate between intermittent photic stimulation which either appears to flicker or appears to be a steady light. The dependent variable is the frequency of flashes at which the change in appearance occurs. A rise in threshold could indicate better sensory processing. A comparison of smokers deprived since the previous night with deprived smokers, who were allowed to smoke a cigarette before testing, showed that smoking increased the threshold slightly (Larson, Finnegan and Haag, 1950). A later study tested a small oral dose of 0.1 mg of nicotine in the form of tobacco powder (Warwick and Eysenck, 1963) and found an elevation of the fusion threshold by about seven per cent. The importance of these changes is difficult to interpret because the finding cannot be related to real life situations. It is believed that the mechanism for critical flicker fusion is at the cortex because alternate flashes to both eyes will produce fusion and so Warwick and Eysenck claim that it is a measure of cortical reactivity rather than sensory processing. In the next section we will be considering the process of attention which is also related to cortical arousal.

In summary, there is little direct or indirect evidence that nicotine improves or impairs sensation to an extent for which it is of practical significance.

b. Attention

Subjective reports from smoking motive questionnaires (eg Russell, Peto and Patel, 1974) indicate clearly that smokers believe that smoking helps them to think and to concentrate. The first piece of experimental evidence to suggest that this experience of enhanced concentration was due to nicotine came from a complex vigilance study by Tarrière and Hartemann (1964) in which subjects performed a main guiding task with a subsidiary visual monitoring task. They counted correct detections of peripheral signals, false detections and guidance errors and said that they measured plasma nicotine and several physiological variables including heart rate and EEG. The test

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groups were non-smokers, smokers deprived for 20 hours and smokers allowed to smoke unspecified cigarettes whenever they wished. Unfortunately they do not give the plasma nicotine levels and their section and graph of "level of nicotine" refers to carbon monoxide. No EEG data are given but an elevation of heart rate, after smoking, indicates some nicotine absorption. Vigilance performance, which was measured in terms of percent omissions, declined in non-smokers and deprived smokers during the 150 minute test but nicotine maintained detection performance throughout the session. No other behavioural data were given on detection errors or guidance errors, presumably because they did not change, but in view of the mistakes in the paper we cannot be certain about this lack of effect. If performance detection had been maintained at the expense of guidance then we could not conclude that concentration was enhanced.

Results which were consistent with Tarrière and Hartmann's study were outlined in a report of smoking and simulated driving (Heimstra, Bancroft and DeKock, 1967). The study will only be mentioned briefly because no physiological measures were taken so the effect of smoking on performance cannot be attributed to nicotine. Heimstra et al studied the effects of smoking and smoking deprivation on brake light vigilance, meter vigilance, steering and brake pedal reaction time. Three groups were used: non-smokers, smokers who were deprived for the six hour test and smokers who could smoke as much as they wished. The consequences of smoking were better performance in comparison with deprived smokers; this effect was manifested as prevention of performance deterioration rather than a performance improvement above control levels.

Frankenhaeuser and her colleagues (Frankenhaeuser, Myrsten, Post and Johansson, 1971) also found that smoking during a prolonged reaction time task enabled subjects to maintain their performance. All subjects were deprived of cigarettes for 10 hours prior to testing. Half of them remained deprived throughout the test while the other half were allowed a 1.4 mg nicotine cigarette after 20 mins, 40 mins and 60 mins of testing. Heart rate increases confirmed that nicotine had been absorbed and the urinary adrenalin levels of the smokers were higher.

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The reaction times for the deprived smokers increased during the course of the 80 minute session while smoking maintained the reaction time. As a group, the smokers also reported that they felt more alert and more relaxed when smoking.

Essentially, the same findings were obtained when the study was repeated using either a similar prolonged test - a low arousal test, or a similar test but with the added stress of two other tasks to be performed at the same time - a high arousal test (Myrsten, Post, Frankenhaeuser and Johansson, 1972, Myrsten, Andersson, Frankenhaeuser and Mardh, 1972). The smokers were sub-divided, on the basis of a questionnaire, into smokers who smoked more often in low arousal situations and those who smoked more often in high arousal situations. Reaction times were better for low arousal smokers who smoked during the low arousal test than when they were deprived but smoking was not beneficial during the high arousal test. The opposite finding was obtained for the high arousal smokers; they only improved with nicotine in the high arousal test. These two studies were the first to reveal that performance was the outcome of a smoking x individual x situation interaction.

In studies at Reading University (Wesnes and Warburton, 1978) smokers deprived for 12 hours and non-smokers were tested on a visual vigilance task which consisted of detecting brief pauses in the minute hand of a clock. Detection performance declined over the 80 minute test in all subjects who did not smoke but deprived smokers who smoked a 1.4 mg cigarette at 20 mins, 40 mins and 60 mins (as in the Frankenhaeuser studies) showed no decrement in detection performance. This experiment revealed that cigarettes helped smokers to maintain better detection performance than either deprived smokers or non-smokers. The two non-smoking groups did not differ significantly so there was no evidence that cigarette deprivation was an important factor. Evidence that this effect was due to nicotine came from a second study with this task using 0, 1 and 2 mg nicotine on alkaline tablets held in the mouth, which enabled buccal absorption of nicotine (Russell and Wesnes, unpublished). The tablets were given to smokers after the same 20 minute intervals as before, in a repeated measure design. During

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the first 20 minutes, performance in the three conditions was matched to give a baseline and a comparison of the three conditions showed a clear dose related improvement after the first and second tablets at 20 mins and 40 mins. However, after the third tablet at 60 mins, performance was worse in the 2 mg group than the 1 mg group. This difference was probably due to the toxic effects of the cumulative dose of 6 mg of nicotine in an hour.

In a third study, cigarettes yielding 0.31, 0.71, and 1.65 mg of nicotine were compared using a version of the vigilance task, with well defined detection intervals and the same experimental design as before. The cigarette butts were analysed to estimate the amount of nicotine which was generated by the smoker. The best group performance, during the first 20 minutes after a cigarette, was obtained after smoking the 0.71 mg nicotine cigarette rather than after smoking the 0.31 mg nicotine cigarette. However, the butt analyses showed that smokers obtained estimated mouth levels of 0.63 mg of nicotine from the 0.31 mg nicotine cigarette, 1.3 mg nicotine from the 0.71 mg nicotine cigarette and 1.5 mg nicotine from the 1.65 mg nicotine cigarette giving evidence of titration. Analyses of individual differences gave clear evidence that subjects who scored high on neuroticism smoked harder at the beginning of the session than low neuroticism subjects while there was some evidence that subjects who scored high on extraversion smoked more intensely at the end of the session than the more introverted subjects. The performance data showed that smoking produced most improvement in subjects with high neuroticism scores. An individual difference analysis of the nicotine tablet study, that was described above, gave similar evidence. Once again, these studies suggest that subjects had a need for nicotine to help them perform within the experimental situation. This need determined the smoking behaviour and performance was the outcome of the interaction of the situation, the individual and smoking.

As well as examining the effects of nicotine and smoking in a long boring task we have also examined sustained attention in a shorter 20 minute rapid information processing test. In a set of eight studies (see Wesnes and Warburton, 1978 and in press) we have tested

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cigarettes of different nicotine deliveries ranging from 0 mg (herbal cigarette) to 2 mg as well as nicotine tablets. The test consisted of a random series of digits, presented individually on a TV screen, at a rate of 100 per min and subjects were asked to respond if they saw a sequence of three odd or three even digits. Eight of these triplets were presented every 10 minutes. Each subject was tested for 10 minutes before a further 20 minutes after a cigarette or tablet. Performance was compared with both the pre-drug baseline and the no smoking, herbal cigarette or placebo tablet conditions. Rather than discuss each individual study only the overall pattern of the findings will be presented. During the three control conditions performance declined over the 20 minute session, in exactly the same way for herbal cigarettes and no smoking, showing that the smoking act itself had no influence on performance in terms of correct detections.

Smoking not only improved performance relative to not smoking but produced an absolute enhancement relative to the pre-nicotine baseline in the first 10 minutes. The absolute enhancement was 11 - 14.5 per cent better than baseline and occurred in 68 - 75.5 per cent of the subjects for each cigarette in each study. In general, a greater improvement was seen after high delivery cigarettes than low delivery products but there was overlap between cigarettes of similar delivery probably due to nicotine titration by the subjects. Conclusive evidence that the better detection performance was due to nicotine came from a study with non smokers using alkaline tablets containing nicotine (Wesnes and Warburton, in press). Doses of 0.5, 1.0 and 1.5 mg of nicotine significatnly reduced the decrement of detection that occurred in the placebo condition and the 1.5 mg dose produced a significant absolute improvement relative to the pre-drug baseline. In this task the stimuli were well above threshold, the memory component was small and the motor response was a simple button press so it can be concluded that nicotine was enhancing either the attentional process, information processing, or both processes.

Support for enhancement of the attentional process comes from a study of nicotine tablets and the Stroop effect. In the Stroop test, subjects name the colours of a set of colour spots and then they are

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presented with a set of colour words printed in another colour. There is a difference between the time taken to read the two sets, known as the Stroop effect, because of the distractions produced by the incongruity between print colour and colour word. Nicotine doses of 1 mg and 2 mg reduced the magnitude of the Stroop effect in both smokers and non-smokers and there was no difference in the size of the effect in smokers and non-smokers. This evidence argues strongly for the hypothesis that nicotine helps a subject to ignore distracting information and concentrate on relevant information.

In summary, this body of data supports the subjective experience of smokers that smoking helps them to concentrate. Correlative physiological and biochemical data together with the nicotine tablet studies indicate that nicotine in cigarette smoke is the agent responsible for this effect. As we have seen, nicotine increases electrocortical arousal and so this work fits neatly with research demonstrating that drugs which modify electrocortical arousal change attentional performance; increases in electrocortical arousal enhance attentional filtering while decreases impair this process (see review Warburton, 1981). In this way nicotine enables subjects to sustain their concentration and filter out distractions.

c. Information Processing

Some evidence for more efficient processing with nicotine came from the early study of Hull (1924) who demonstrated that nicotine, from pipe smoke, decreased reaction time and improved addition speed. This finding was supported by a study of cigarette smoking and simple reaction time (Fisher, 1927). It could be argued that, in simple reaction time studies where subjects only have to decide if a light is present, the information processing component is small, but faster addition without loss of accuracy would seem to support the hypothesis of greater processing efficiency.

The studies of smoking and nicotine tablets and rapid information processing (Wesnes and Warburton, in press) provide unequivocal evidence for more efficient processing when using cigarettes or tablets with nicotine. As we have seen, both cigarette smoking and nicotine tablets

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improved detection of the triplets of three odd or three even digits in a string of single numbers flashed on a computer screen. The reaction times of these detections were also recorded and it was found that nicotine from cigarettes and tablets reduced reaction time. The reaction time improvement was around seven per cent and between 65 and 77 per cent of the subjects were improved depending on the nicotine delivery of the cigarette. This finding is very important because it shows that there is no trade-off between speed and accuracy and there was an overall improvement in processing efficiency.

This behavioural data fits neatly with the study of Edwards et al (in press) which showed that smoking decreased the latency and amplitude of the P300 wave of the event related potentials in the rapid information processing task that was referred to previously in Sub-section IV C3. In this study the behavioural data also showed faster reaction time and improved detection of the odd and even triplets of digits. Thus both behavioural and electrocortical measures indicate that nicotine is enabling more efficient processing of information in the brain.

In summary, the evidence from this section and the last section are consistent in showing that nicotine by its action at the cortex of the smoker produces better information selection and faster, more accurate evaluation of that information.

d. Learning and Memory

The effects of nicotine on learning have been investigated most extensively by Karin Andersson. The first study, (Andersson and Post, 1974) compared the effect of nicotine-free cigarettes and nicotine cigarettes on learning a nonsense syllable list on light smokers (less than five per day) who were deprived for 12 hours prior to the testing. On the first test day subjects always smoked a 2.1 mg nicotine cigarette and on the second day subjects were given a nicotine-free cigarette. Significant increases in heart rate showed that the subjects were absorbing nicotine from the nicotine cigarettes. The first cigarette was given after the first ten trials of learning the list of nonsense syllables and a second cigarette, of the same

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kind, was given after 20 trials; trials were given every two minutes. The learning curves were identical for the two conditions prior to smoking, but after smoking, the number of correct syllables decreased when the subjects had the nicotine cigarette and remained below the performance in the nicotine-free condition although the learning curves were parallel. After the second nicotine cigarette, the number of syllables correctly repeated increased significantly and reached the same level of acquisition performance as in the nicotine-free cigarette condition. Thus, relative to the previous performance, nicotine had improved recall of the syllables. These data give no evidence of nicotine impairing learning because the learning curves are parallel after the nicotine cigarette. It was as if the information stored in the non-nicotine state was less available in the drug state, a phenomenon known as state-dependent learning. We will return to tests of this possibility later.

In a related study using nonsense syllables (Andersson, 1975 a) a similar learning procedure was used in which subjects smoked either a high nicotine cigarette (2.1 mg) or did not smoke after the tenth trial. Heart rate changes indicated nicotine absorption in the smoking condition. After trial 20 there was an interval of either 8 minutes or 45 minutes when subjects were given a jigsaw puzzle to solve to prevent rehearsal. Then, a single recall trial was given 26 or 65 minutes after smoking. Performance on trials 1-10 were the same for the smoking and no smoking conditions, nicotine decreased recall on trials 11-20 although did not affect the rate of acquisition. After 8 minutes there was poorer recall in the nicotine condition ($p<0.05$), while after the 45 minute interval there was some evidence ($p<0.10$) that recall was better after nicotine than no nicotine. The slight superiority of the nicotine group shows that the decrement in performance, after trial 10, could not be due to an impairment of information input and storage by nicotine and there could even have been an improvement of one of these processes. From the earlier discussion we can hypothesise that this effect could have been due to more efficient input of information after nicotine, and the impairment after trial 10 due to a change of state. The difficulty of interpreting the effects of nicotine in this study,

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and in the last one is that learning and recall are occurring over a 20 minute period while plasma and brain levels of nicotine fall by a half.

In a third study, relating nicotine and recognition memory, Andersson (1975 b) tested smokers on recognition of previously presented numbers. A set of the numbers 1-25 were randomly presented to the subjects who were required to respond if they remembered that they had seen a number before. Three sets of numbers were given so that the task became more complex as the test proceeded. There was a high nicotine cigarette (2.3 mg), a low nicotine cigarette (0.37 mg) and a no smoking condition. Heart rate increases indicated absorption of nicotine from the cigarettes. No statistically signficiant differences ($p<0.1$) were obtained but on the first number, set recall was better in the no smoking condition than in the low nicotine condition, and recall was worst in the high nicotine condition. On the second and third number sets the order was reversed ie better recognition after smoking. These trends on the last two sets can be interpreted in terms of nicotine improving information processing by enabling the subjects to select the 'relevant' information (the digits of the present set) from the irrelevant (the digits presented in the previous set or sets).

The final study of Andersson (Andersson and Hockey, 1977) used a memory test that consisted of relevant and irrelevant information which enables this selectional interpretation to be examined further. A list of eight Swedish adjectives were presented, one at a time, in one of the four corners of a screen and the subjects were told that they would have to write down the words in presentation order ie the words and their order were relevant and by implication location was irrelevant. Two groups of smokers, deprived of cigarettes for 12 hours, received either a high nicotine cigarette (2.3 mg) or remained deprived. There were no differences between the nicotine and no nicotine groups for percentage of words that were recalled in the correct order, or for the percentage of words that were recalled correctly regardless of word order. This finding contradicts Andersson's previous evidence on recall. The most interesting

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finding was the decreased amount of irrelevant information recalled with nicotine; positions on the screen were recalled significantly less well with a group recall score of 30.2 per cent, which is only just above the chance level of 25 per cent. In a second test, in which subjects were required to remember words, word order and screen position, the groups did not differ significantly in their recall although there was a trend for location to be recalled better after nicotine (62.2 per cent) than when deprived (55.3 per cent). These data on recall also contradict the previous findings. This study suggests that nicotine can enable more limited and selective processing of information but it should be noted that the effect only occurs when the information is thought by the subjects to be incidental and not when the subjects were asked to remember it ie nicotine is not acting on a passive system.

In the earlier discussion the possibility of nicotine producing state dependent learning in human subjects was mentioned and numerous animal studies have given evidence of state dependency with cholinergic drugs (see review in Warburton, 1977). In a state dependent design one group of subjects learns after a drug dose while a second group learns after a placebo or no drug. For the recall test both groups are divided in two, one half of each group are tested with the drug of learning and half are switched to the other condition. If the recall scores are better for those groups which had the same drug state, then state dependent learning is said to have occurred. This state dependency hypothesis with nicotine has been investigated in several studies.

In the first published study (Houston, Schneider and Jarvik, 1978) 23 heavy smokers, deprived of cigarettes for three hours, read a list of words and were then given a free recall test prior to smoking in order to match the groups for learning ability. One group smoked a 1.5 mg nicotine cigarette and the other group smoked a non-nicotine cigarette. Smoking behaviour was controlled by asking the subjects to puff 12 times at thirty second intervals and to inhale and hold the smoke in their lungs for five seconds before exhaling. Although puff volume, puff duration and depth of inhalation were not controlled,

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the procedure would make it more likely that a relatively uniform amount of nicotine was absorbed by the group. Controlling the dose in this way makes the study pharmacologically sophisticated but it may be nonsensical from the point of view of the smokers, who would prefer to titrate for their own dose.

After this controlled smoking procedure, the subjects were given three successive lists with free recall tests after each one. The immediate recall scores showed that the nicotine group had significantly poorer recall than the placebo group although their pre-smoking scores were not different. These findings match those of Andersson and Post (1974) and Andersson (1975 a). Forty eight hours later, eight of the subjects from each condition returned for retesting and were sub-divided giving four groups of four subjects. They smoked either a nicotine or a non-nicotine cigarette as before, followed by another free recall test of all the lists. Once again the recall scores of the subjects, who smoked a nicotine cigarette at the time of learning, were significantly worse than those who smoked a non-nicotine cigarette which was not consistent with the findings of Andersson and Post (1974) and Andersson (1975 a). No evidence of state dependent learning was obtained, ie the group receiving a nicotine cigarette or a non-nicotine cigarette on both learning and recall did not have better scores than subjects who switched their cigarettes. However, with such small groups it is not surprising that no differences were found.

In contrast with the last study, two more studies have found positive evidence for state dependent learning with nicotine (Warburton, Wesnes and Shergold, 1982). The first experiment used the state dependent design to test nicotine's effect on recognition memory. Forty smokers, who were deprived of cigarettes for 10 hours, were given a 1.4 mg nicotine cigarette or allowed to relax immediately before serial presentation of a set of 30 Chinese radicals. After presentation, the subjects were allowed to read for one hour until the recognition recall test when they were divided into four groups - no smoking prior to learning and recall; no smoking prior to learning but a cigarette prior to recall; a cigarette prior to learning and recall; and a cigarette prior to learning but none prior to recall.

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Subjects who received nicotine prior to learning had significantly better recognition scores than the subjects who did not smoke in the first part of the experiment. There was no effect of nicotine on recall performance. A significant interaction term indicated that changing drug state interfered with recognition.

A more elaborate study examined the effect of a controlled dose of nicotine on short-term and long-term recall, within the framework of a state dependent design. Subjects, who were smokers deprived of cigarettes for ten hours, held a 1.5 mg alkaline nicotine tablet (pH 9) or a placebo tablet in their mouth for five minutes to allow nicotine absorption, tablets were then swallowed. Buccal and gastric absorption would be expected because of the alkaline tablet and this combination produces plasma levels of nicotine which remain stable for 30 mins (Russell and Wesnes, unpublished). After the tablet, the subjects listened to a list of 38 words and then did successive subtraction of seventeen from a larger number for one minute to prevent rehearsal. A free recall test was given for 10 minutes and then the subjects were allowed to leave the test room but were told that they would be called in 1 hour for a second, unspecified test. They were instructed not to smoke in this interval. During the hour they worked and were then recalled, given either nicotine or placebo tablets, depending on their group, and asked to recall as many of the words as they could in another 10 minutes free recall test.

The short term recall data revealed a very significant superiority of the nicotine group over the placebo group. Long term recall was also significantly better when subjects had taken nicotine prior to learning but not when taken prior to recall. The very significant interaction term again gave evidence for a state dependent effect of nicotine and showed that nicotine was facilitating the input of information to storage but had no direct effect on storage or retrieval. These findings are consistent with previous results which showed that nicotine facilitated information processing. However, the state dependency effect, for which there was some evidence in the studies of Andersson and Post (1974) and Andersson (1975 a), resulted in a poorer recall when subjects either learning with nicotine but recalled without nicotine or vice versa. In view of the previous discussion of

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nicotine's effects on information processing, a state dependent effect is not surprising because of the differences in the selection and processing of information due to nicotine increasing electrocortical arousal. A large body of literature has demonstrated that recall is better when the learning and recall situations are identical.

In conclusion, these studies show that in some circumstances nicotine can enhance the storage of information, probably because of more efficient input of information, but recall may be less efficient if the person is tested without nicotine. For habitual smokers this impairment would only be likely if they were deprived of cigarettes. It should be emphasised once again that this conclusion agrees with animal studies of learning with nicotine and with studies of cholinergic drugs and learning in general.

e. Motor Output

There is no evidence of gross changes in motor output after smoking doses of nicotine or nicotine tablets and the only change is a reliable increase in hand tremor after smoking (Larson et al, 1950). Although nicotine does act directly on neuromuscular junctions, (see sub-section IV B1) the tremor seems to be due to an effect on the central nervous system as well, perhaps at the level of the motor regions of the mesencephalic reticular formation. This fine tremor seems to have no practical significance except that it can be used as a marker for nicotine absorption.

f. Conclusions

Smokers report that they smoke to help them think and concentrate and the experimental evidence supports this rationale. Smoking and nicotine produce better selection of information from the environment and faster processing of that information which is reflected in improved attention and learning. There is some evidence that the improved learning by nicotine does not always transfer completely to the deprived condition and recall is partially impaired. This change probably has little significance for the habitual smoker who maintains plasma nicotine levels above some minimum level. The

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changes in sensory thresholds and hand tremor are inconsequential for most smokers.

2. Mood States

A large number of studies relating nicotine and mood have been carried out and so this review will be illustrative rather than exhaustive. It will focus on the mood states rather than the method of investigation and will discuss whether smoking does have sedative effects on anxiety and anger as smokers claim. In most cases the experimental studies have provided no evidence of nicotine absorption from cigarettes, and therefore it is not usually possible to separate the sedative effects of nicotine from the calming effect of the smoking ritual of cigarette manipulation.

a. Anxiety

Evidence for a sedative action of smoking comes from questionnaire studies, stress studies, personality tests of smokers and non-smokers, smoking abstinence studies and situations affecting smoking behaviour.

In a smoking motives survey, McKennell (1970) asked smokers about their mood states which might tempt them to smoke a cigarette and factor analysed the answers to extract the major factors which would produce smoking. One of these factors was "nervous irritation" smoking which included "smokes when anxious or worried" and "smokes when nervous" and also "smokes when angry". When the number of cigarettes smoked was controlled, female smokers exceeded the men for "nervous irritation" smoking. A factor analysis of smoking situations by Frith (1971) found a similar factor which he called high arousal smoking. High arousal smokers had a strong desire for a cigarette in stressful situations (eg an important interview) and women were more likely than men to smoke in these situations. Using a Smoking Motives Questionnaire, Russell et al (1974) and Warburton and Wesnes (1978) found that 93 per cent of smokers who attended a smoking clinic, 74 per cent of non-clinic smokers and 88 per cent of students said that they smoked when worried. Altogether, this evidence shows that smokers believe that smoking is beneficial to them when they are anxious.

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The bulk of the experimental evidence for smoking helping in stress situations has come from Stanley Schachter's laboratory. Nesbitt (1973) tested smokers, who used 20 or more cigarettes a day, and non-smokers on a shock tolerance test, on the assumption that it provided a measure of anxiety. Both groups were asked to smoke a 1.6 mg or 0.3 mg nicotine cigarette or puff on an unlighted cigarette. It was found that smokers who were smoking could take up to 2,450 microamps more after smoking and this effect was dose dependent. On the other hand, the non-smokers tolerated more shock in the no smoking condition but slightly less after the high nicotine cigarette. Assuming that shock tolerance is a measure of anxiety the simple explanation that smoking reduces anxiety does not fit this data because smokers who were only allowed to puff an unlighted cigarette tolerated less shock than non-smokers in the same condition. The latter finding suggests that nicotine from the smoke is more important than the smoking ritual in the effect on anxiety, but also that absence of nicotine in smokers results in more anxiety than for non-smokers. This finding could mean either that a nicotine deficit results in abstinence symptoms due to physiological dependence on nicotine or that smokers are constitutionally more anxious.

The latter possibility can be examined from personality studies of smokers. One influential theory of individual differences in behaviour is based on the dichotomy between extraversion and introversion and between neuroticism and stability and can be measured by a questionnaire such as the Eysenck Personality Inventory (Eysenck and Eysenck, 1964). People having high scores on neuroticism displays labile, emotional behaviour and are anxious, irritable, moody, restless, excitable and changeable. In contrast, stable people are calm and even tempered. There is less consistency in the evidence for a relationship between smoking and neuroticism, and Eysenck's studies of 6,000 men gave no evidence for a significant correlation (Eysenck et al , 1960; Eysenck, 1963 a). Rae's (1975) survey of 253 female students revealed no differences in the degree of neuroticism between non-smokers, ex-smokers, light smokers or medium smokers, but there were very few heavy smokers (over 15 per day) in his college sample. However, at least seven studies have suggested a positive relationship of smoking with neuroticism and this association is particularly strong for

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women smokers (Meares, et al, 1971; Waters, 1971; Dunnell and Cartwright, 1972).

In research at Reading University (Warburton, Wesnes and Revell, 1982) a questionnaire was given to 250 student male and female smokers to obtain information about the number of cigarettes smoked a day, the number of years that the individual had been smoking and the specific brands smoked. All the smokers completed the Eysenck Personality Inventory as well. Analysis of the data on number smoked per day and level of neuroticism of the whole group disclosed no association of smoke with neuroticism. However, for both sexes the distribution of number of cigarettes per day was bimodal with a separation around 15 cigarettes per day, in agreement with the results of a survey by Schachter (1978). This distribution suggests that there are two populations of smokers, light smokers and heavy smokers, as far as number of cigaretes smoked is concerned. The personality and smoking data were analysed separately in four groups, defined by sex and whether they were heavy or light smokers, so that the correlations within each of the four groups could reveal associations which may exist between smoking and neuroticism level. A positive correlation was found between the number smoked per day and the degree of neuroticism (ie the more neurotic smokers in each group smoked more cigarettes per day), even though the mean neuroticism scores of light and heavy smokers did not differ. Thus neuroticism was not related to whether a smoker was either a heavy smoker or light smoker, but within each sub-population, the number that he or she smoked per day was related to the degree of the individual's neuroticism. The heavy smokers were more extraverted than the light smokers and within each of these groups the male smokers were less extraverted than the females. In brief, light or heavy smoking was associated with extraversion, but within these two sub-populations, the number smoked per day was associated with neuroticism.

From these data one can speculate that the constitutional factors, which result in extraverted behaviour, determine whether a person becomes a light or heavy smoker whereas the factors that underlie neuroticism are not associated with heavy or light smoking, but influence the number smoked per day if an individual is a light or heavy smoker.

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Another interesting relationship emerged when correlations between personality and cigarette strength were considered. While extraversion scores were not correlated with the strength of cigarettes smoked, neuroticism scores were positively correlated for women, uncorrelated for male, light smokers and negatively correlated for male, heavy smokers so that the more neurotic females smoked higher delivery cigarettes.

Of course, these correlations were based on the machine-estimated yields of the cigarettes smoked and do not tell us how much nicotine was actually absorbed by the smoker. Self-report of depth of inhalation also varied among the personality groups. Deep inhalers had a higher mean neuroticism score than slight inhalers whose neuroticism scores were the same as non-smokers which suggests that smokers who score high on neuroticism absorb more nicotine.

In summary, we can safely conclude that the strength of cigarettes that are purchased by women smokers is related to their degree of neuroticism, and from the whole body of survey data that women buy cigarettes in order to help them cope with neuroticism.

Although this evidence is persuasive, Schachter might still argue that repeated exposure to nicotine had caused anxiety and a higher neuroticism score. Evidence against this argument is the lack of an overall correlation between number smoked and neuroticism. A second piece of evidence comes from a crucial study done by Cherry and Kiernan (1976; 1978) which has followed a cohort of 2,853 young people for 25 years. When they were 16 years old the subjects completed the Maudesley Personality Inventory before most of them had begun to smoke. At 20 years and 25 years of age they completed a smoking habits questionnaire and it was found that the cigarette smokers, as a group, were more extraverted and neurotic as we would have expected and those teenagers who smoked regularly before 16 years of age were more neurotic and more extraverted than smokers who did not smoke before they were 16 years old. A statistical analysis revealed that the two personality dimensions are independent and additive in their effect on the likelihood of becoming a habitual smoker and indicated that the constitution factors underlying anxiety produce smoking and not the other way round.

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As was pointed out earlier (Section III D) smokers can titrate for nicotine by varying the number of cigarettes smoked, their patterns of puffing and the amount of smoke inhaled. From these findings it can be predicted that smokers should titrate for nicotine depending on the situational demands, if they are smoking for nicotine to reduce anxiety. Schachter (1978) described two studies in which he studied stress and the number of cigarettes that were smoked. The subjects were tested with electric shock ostensibly to determine their tactile sensitivity. In the low stress condition smokers only received a low level of current to produce a tingle while the high stress group were occasionally given a painful shock. Schachter counted the number of cigarettes smoked between tests in the laboratory and found that the subjects smoked more cigarettes in the interval after the high stress condition than after the low stress condition ie when they were anxiously anticipating the next test series. Unfortunately, he did not collect any information about smoke generation and smoke manipulation.

In a recent study (Warburton et al, 1982) 48 first year undergraduates filled in a detailed diary on their smoking habits during a first year examination period and again 6 weeks later, after the examination results had come out. This design enabled us to compare the smoking behaviour of students in a high stress and a low stress period of their lives and find how people adjust their cigarette intake according to the situation. From the cigarette totals for the afternoons and evenings it was obvious that subjects smoked significantly more cigarettes at all times during the examination period than six weeks later. The mean number of cigarettes smoked during the morning before an afternoon examination was 80 per cent above the average number for mornings during the non-examination period and had increased by 29 per cent over the mean morning consumption for the examination period as a whole. The mean number of cigarettes smoked in an evening before an examination was higher than the mean for evenings in the non-examination period.

Subjects gave a subjective evaluation of their degree of inhalation and these reports followed exactly the same pattern as the data for number of cigarettes smoked ie, highly significant increases in degree

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of inhalation during the examinations with respect to the post-examination period. There was greater inhalation during the morning before an afternoon examination compared with the mean for mornings of the non-examination period. The degree of inhalation for the evening before a morning examination was significantly higher than the mean for an evening prior to a free day. Similarly, a comparison of the evening before a free day, within the examination period, with the mean for evenings, in the non-examination period, gave significant differences for degree of inhalation. Once again the individual data are highly consistent.

Thus the undergraduate students who took part in this study increased the number of cigarettes that they smoked quite dramatically when faced with examinations and the concomitant stress. They also felt that they were inhaling more than during the non-examination period. It can be assumed that the two questionnaires were fairly independent since the first was completed and returned six weeks before the second.

Some experimental evidence for titration by puffing was found by Ashton and Watson (1970) with subjects smoking in a driving simulation task. Subjects were tested in an easy driving task, a stressful driving task and at rest. In all situations they found that subjects puffed more frequently at the medium nicotine cigarettes (1.0 mg of nicotine on machine-estimated delivery) than the high nicotine cigarettes (2.1 mg nicotine on machine-estimated delivery), and butt analyses revealed that they took into their mouths nearly the same amount of nicotine from each brand. Interestingly, subjects generated more nicotine from the cigarettes during the more stressful test than the easier test, although the differences were not statistically significant, which suggests that individual smokers titrate the nicotine delivery from the cigarette according to the situation.

The Reading University research programme has examined the situation x individual x smoking interaction by studying the amount of nicotine taken by subjects in the vigilance test mentioned earlier (Warburton and Wesnes, 1978). Correlations were made between the neuroticism scores and the butt nicotine level from the test cigarettes. There was some evidence that the more neurotic subjects puffed harder than the more stable subjects on the first cigarette of

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the test period. However, a more interesting association was found between neuroticism and the change in smoking pattern over the session. A positive correlation was found between neuroticism and the difference in smoke generation between the first and last cigarette for both the low nicotine cigarette and the high nicotine cigarette, indicating that the more neurotic subjects smoke more intensely at the beginning of the session than at the end of the test. This result provides further evidence that one aspect of smoking behaviour is the outcome of the interaction of the situation and the individual.

Anxiety arises in situations of uncertainty when a person is subjected to an unpredictable pattern of stimuli or is faced with uncertainty about which response to choose, or both (Warburton, 1979) and this effect will be greater in more neurotic subjects in our test situation. Consequently, it can be argued that the more neurotic subjects found the test situation particularly stressful, and so they smoked more intensely because they have a greater need for nicotine in order to cope with the experimental test. This result is consistent with the trend in the data of Ashton and Watson (1970) that stress increased smoking intensity.

This research strongly suggests that smoking behaviour changes in stressful situations; smokers use more cigarettes, smoke them more intensely and inhale the smoke more deeply. The more neurotic subjects (those who are more anxious and susceptible to stress) show the most marked effects. The interesting question is: Does smoking help to cope with stress and improve behavioural efficiency? Accordingly we have analysed performance increments as a function of neuroticism and found that there was a direct association between the degree of neuroticism and the amount of performance improvement (Warburton and Wesnes, 1978). The latter association is consistent with data obtained by Kucek (1975) in an experiment where subjects were tested under conditions of information overload in which they were required to track a target and do mental arithmetic. A comparison of neurotic smokers allowed to smoke and neurotic smokers not smoking showed that smoking had a beneficial effect on the performance of neurotic subjects allowed to smoke.

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Nicotine is the most likely constituent of cigarettes for producing this improvement in performance, and in another vigilance study we tested nicotine tablets containing doses of nicotine in the range of those estimated as entering the smokers mouth in the previous study. For both females and males the improvement-scores were directly correlated with neuroticism (Warburton and Wesnes, 1978). This signficiant association with neuroticism gives strong evidence for the hypothesis that nicotine is the sedative ingredient of cigarette smoke which is beneficial for performance, especially for the more neurotic subjects.

Inferences about the properties of a drug can often be made from the symptoms that occur when medication is terminated; for example the function of insulin for a diabetic person can be inferred from the symptom that occurs when injections are discontinued. Studies of withdrawal symptoms that follow cessation of smoking show that one of the major symptoms of cigarette withdrawal is anxiety (Nesbitt, 1973; Shiffman and Jarvik, 1976). It is more likely to occur among women because in this group there is a greater proportion of neurotic smokers (Guilford, 1966; Shiffman, 1979 b). Anxiety is also given as one of the major causes of relapse, especially among women (Shiffman, 1979 b). An analysis of the situations which resulted in a return to smoking was made by Marlatt (1979) and Shiffman (1971 a). Retrospective reports indicated that 80 per cent of these situations fell into three categories: coping with anxiety and other negative emotional states (43%), social pressure (25%) and coping with social stress (12%). Few of Marlatt's and Shiffman's relapsed smokers reported that physical withdrawal symptoms triggered the relapse which argues against the hypothesis that smokers carry on smoking because of physical dependence. In the Shiffman (1979 a) study, two thirds of the subjects were under stress at the time of relapse and anxiety was particularly common among ex-smokers who relapsed at work, which suggests that work-related anxiety was a contributory factor. Neurotics are more anxiety-prone and so it is not surprising that this group find it difficult to stop smoking or relapse if they do abstain (Cherry and Kiernan, 1978). These data on smoking to cope with stress fit neatly with studies which suggest that deprived smokers, as a group, are more likely to respond with anxiety in situations in which they are stressed. (Frankenhaeuser, et al, 1971; Myrsten, et al, 1972; Schachter, 1978).

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A large epidemiological study of British doctors has given some evidence which may indicate there are adverse consequences of smoking cessation (Lee, 1979). As a group, doctors have reduced their cigarette smoking over 20 years, and there has been some of the expected improvement in mortality rate from the so-called "smoke-related" diseases, but the overall death rate did not fall as much as one might have predicted from other groups of similar socioeconomic status. The reason for this discrepancy is that mortality from other causes has increased. In particular, stress-related deaths have increased relative to other professions in the equivalent social class, and more doctors have died from accidents, poisonings, suicide, and cirrhosis of the liver. Lee concludes that "the relative worsening in mortality from stress-related diseases may have been due partly to a possible adverse effect of giving up smoking if smoking had acted to reduce stress" (p 1538). This conclusion must be treated with caution because it is always very hazardous to argue from correlation to causality but, nevertheless, it is consistent with the previously cited research on smoking and stress.

In summary, a large body of evidence indicates that smokers smoke to reduce anxiety and smoke more and presumably take more nicotine when under stress. Subjects who are more prone to anxiety, ie scoring high on the neuroticism scale, smoke more intensely. Some experiments show that nicotine helps them cope with the situation better. Ex-smokers report that anxiety is one of the major problems of cessation and there is evidence that stress can lead to relapse. Those smokers who do abstain seem to be more prone to stress-related disorders and the full benefits of stopping smoking in terms of decreased mortality may not be achieved.

b. Anger

Another item that made up the "nervous irritation" factor of smoking in the McKennell (1970) questionnaire was anger. Thomas (1973) reported that on her "habits of nervous tension" questionnaire cigarette smokers and former smokers had higher levels of irritability and anger in comparison with lifetime non-smokers. When

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the smokers were divided into light (less than 20 a day) and heavy groups, the heavy smokers showed greater anger under stress than the light smokers. In two studies of smokers at a stop-smoking clinic and non-clinic smokers (Russell et al, 1974) and student smokers (Warburton and Wesnes, 1978), smoking when angry was one of the "top 10" reasons given for smoking by smokers attending a stop smoking clinic (83 per cent), non-clinic smokers (47 per cent) and student smokers (65 per cent). It appears from this consistency that a feeling of anger is a motive for smoking in some people.

Experimental studies of anger are difficult to conduct and no satisfactory experiments on nicotine and anger in humans have been done. Schachter (1978) reports a study by Perlick which compared irritability in groups of "unrestrained" and "restrained" smokers the latter were trying to cut down their smoking and smoked less of the cigarettes. Each group were then exposed to aircraft noise and asked to rate the annoyance caused by the noise, after smoking either a 1.3 mg nicotine cigarette, a 0.3 mg nicotine cigarette or not smoking. It was found that unrestrained smokers, when deprived or smoking the low nicotine cigarette, were more annoyed than when smoking the medium nicotine cigarette. However, unrestrained smokers, when smoking the medium nicotine cigarette, were no better than non-smokers. The restrained group were just as irritated in all three conditions as the deprived or low nicotine, unrestrained smokers. There are at least two explanations for these results; either irritability is an abstinence symptom which is the consequence of nicotine dependence, or smokers are constitutionally more irritable and nicotine from smoking helps to reduce this feeling.

Studies of abstinence have shown hostility and aggressive behaviour increase markedly during abstinence (Mausner, 1980; Schachter and Rand, 1974; Shiffman and Jarvik, 1976). Anger is commonly reported as a factor triggering relapse among ex-smokers, and these relapses occurred in the absence of smoking-related cues such as "people around were smoking". (Shiffman, 1979 a). Clearly, the smoker who is deprived of nicotine is less calm. Evidence from a study by Thomas (1973), which showed similar scores for anger when stressed for smokers and ex-smokers, suggests that smokers are constitutionally more angry and irritable.

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In summary, smoking, and by inference nicotine, seems to have sedative effects for anger as well as anxiety.

3. Conclusion

These findings of enhanced psychological efficiency after nicotine are interesting from a psychopharmacological point of view because, although many drugs impair performance, it has proved difficult to find drugs which produce real improvements or even sustain performance in healthy, well-motivated subjects. The finding that nicotine can also act as a sedative makes the enhancement even more interesting because drugs with anti-anxiety action usually impair performance at effective doses. Thus nicotine is a unique substance because it combines both performance enhancement with anti-anxiety and anti-anger action.

While these findings alone are interesting, they assume even greater significance when they are considered in the light of the smoker's precise personal control over nicotine intake. The data in the preceding sections can be combined to argue that cigarette smoking can be regarded as self medication for certain groups. Studies of self medication suggest that people use those classes of drug which fulfil their own individual needs (Warburton, 1978) and the research presented here shows that people titrate nicotine to obtain a specific dose to fit their needs. Depending on the situation, smokers will adjust their smoking behaviour in terms of the number of cigarettes smoked, smoke generation and amount of smoke inhaled to control the nicotine levels reaching their brain and in this way their psychological state. Deprivation of cigarettes results in marked abstinence symptoms which are manifested as less efficient functions in certain situations, and so relapse is likely to occur in these contexts.

Consequently, the behaviour of a smoker is the outcome of a complex set of interactions. It is obviously determined, not only by the characteristics of the situation, but also by the personality of the individual. The personality characteristics will determine the way in which the individual selects and interprets information within the situation ie there is an interaction going on between individual factors

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and situational factors. If it is assumed that individual differences have a constitional basis (ie differences in the neurochemical pathways in the brain) then another complex interaction occurs when a drug is given to a person. Drugs do not affect human performance directly, but they produce changes in behaviour as a consequence of their interaction with endogenous chemicals within the body. Changes in neurochemical activity in the brain alter the way in which a person interacts with his environment and so performance not only reflects the nature of the drug but also the biochemical state of the person at that moment.

In sections (a) and (b) we have discussed the "stimulation" (low arousal) smoker and the "sedative" (high arousal) smoker as if they were homogeneous groups who self-medicated in the same way all the time. However, there must be differences in smoking behaviour as a function of the intensity of the individual-situation interaction, its duration and more probably its density (the product of intensity and duration). For example, a stimulation smoker may need less nicotine in brief, slightly boring tasks than a prolonged tedious situation, but conceivably the same smoking behaviour could occur during a brief, very boring, experience and a long, but moderately interesting task. In other cases smoking may not even be initiated until the intensity, duration or density of the interaction is at a critical level. Clearly, lighting a cigarette and the pattern of smoking behaviour depends on the individual-situation interaction.

An important extension of these concepts can be made on the basis of the observation that some smokers smoke in anticipation of a future need, before the situation has occurred or the critical stress level has been reached, and they are still coping. Here the smoking behaviour is very clearly a response to the individual's interpretation of the situation, his expectations about what may occur, rather than the objective characteristics of the situation. Smokers have learned that self-medication by smoking will enable them to function more efficiently on some tasks and will help them avoid the undesired consequences of other situations and so anticipatory smoking can be seen as a rational coping strategy on the basis of their past experience.

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Advocates of abstinence and the operators of stop smoking clinics have disregarded this information. They have focused on the smoke-related diseases and not considered the benefits of smoking. The smoking habit must be considered from the point of view of the smoker. If he smokes and absorbs nicotine he will function more efficiently now, but risks impaired health in the future. If he abstains he loses the benefit of nicotine and may have better health in the future. It is not surprising that many smokers choose to continue smoking, that abstaining smokers relapse, and stop smoking programmes have a conspicuous lack of success. In the next section we will consider nicotine in the context of some other substances which have been used by people to control their mood or to help them perform better.

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V. NICOTINE USE IN PERSPECTIVE

1. Introduction

When evaluating nicotine use and the smoking habit it is important to compare nicotine with other substances which are habitually used and compounds which produce similar effects. Comparisons with reference substances are an essential part of the assessment of any therapeutic agent so that the relative costs and benefits can be estimated and decisions made about the agent's usefulness. In the case of nicotine, which has stimulant and sedative properties, the selected reference agents are the psychostimulants, amphetamine and caffeine, and the sedatives, diazepam (Valium) and alcohol. In addition we have also included marijuana (active ingredient is Δ^9-tetrahydrocannabinol or THC), which is inhaled for its pleasurable effects.

The comparison takes the form of an analysis of both the pharmacokinetic and pharmacodynamic features of these substances which could constitute risk to the user. The important pharmacokinetic features are absorption, user control of dose, duration of action, side effects that would impair normal functioning (acute toxicity), chronic toxicity in terms of damage to brain and body, and abuse potential.

2. Absorption

As we have seen, nicotine inhaled into the lungs, is readily absorbed and travels from the pulmonary vein to the brain within ten seconds to reach peak concentration immediately after the last puff of the cigarette, ie about seven minutes after lighting up (see Section II). An oral dose of alcohol must travel through the stomach, where some absorption may occur depending on the stomach contents, to the major site of rapid absorption in the small intenstine. Gastric emptying time and thus the onset of absorption results in a variable rate of uptake so that peak concentrations of alcohol in plasma are reached between 40 minutes and 120 minutes (Lemberger and Rubin, 1976). Diazepam is also absorbed from the

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gastrointestinal tract and several hours are needed to achieve peak blood and brain levels (Kornetsky, 1976). Amphetamine and caffeine are absorbed from the stomach and peak concentrations in plasma and brain are reached about 30 minutes after an oral dose of caffeine (Marks and Kelly, 1973) and between one and three hours after an oral dose of amphetamine (Beckett, 1970). Amphetamine is also taken intravenously and peak doses in the brain can be achieved within five minutes (Lemberger and Rubin, 1976). The absorption of THC into the bloodstream is rapid when inhaled and it passes rapidly to the brain, but uptake into the brain is slow so that only one per cent appears in rat brain at 60 minutes (Lemberger and Rubin, 1976). Obviously, nicotine reaches potential active sites in the brain very quickly in comparison with these reference substances.

Absorption time is significant for personal control of effect and prevention of over-dosing; a fast absorption time enables the user to adjust his dose to his requirements and so control the magnitude of effect. An ideal agent for self-medication would enable the person to fit the dose to his needs. Smokers have puff by puff control with brain effects occuring within 10 seconds while a drinker must choose an "appropriate" dose for effects in an hour or so. Thus in terms of personal control the experienced smoker has precise control over nicotine's psychoactive effects whereas most drinkers have very haphazard control. Precision of control is also particularly important when considering toxicity because the risk of exceeding the optimal dose is minimised.

3. Duration of Action

A second aspect of pharmacokinetics, which is also related to personal control of a person's psychological state, is duration of action. Psychological needs vary and most people want coping techniques for specific occasions rather than for chronic states. Thus stimulation may be needed for an arduous task but not some hours later at bedtime; anxiety reduction is required for a 10 minutes interview with a director but not for interacting with colleagues.

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Nicotine has a half-life of only 20 minutes and is cleared from the body in about 40 minutes (see Section II). In comparison, alcohol (Beckett, 1970) and caffeine (Marks and Kelly, 1973) have half-lives in the range of 3-4 hours and both may remain in the body for 8-12 hours (Gilbert, 1976). Although these values are several orders of magnitude more than for nicotine they are insignificant in comparison with the 20-50 hours for the elimination half-life of diazepam (Breimer, 1979) and 56 hours for THC (Lemberger and Rubin, 1976). In addition, diazepam and THC have active metabolites that further prolong their action while cotinine the major metabolite of nicotine seems to be virtually inactive.

Clearly nicotine fits the pharmacokinetic specifications of a compound which a person can use to self medicate and exert fine control over his psychological state on an hour by hour basis.

4. Specificity of Action

One of the important pharmacodynamic criteria for a therapeutically useful agent is that it is relatively specific in its mode of action. Ideally it should be a "magic bullet" that moves specifically to the target site and exerts its action at no other loci. Much more common among psychoactive substances are those which act on several biochemical systems even at low doses. The acetylcholine, dopamine, noradrenalin and serotonin systems are all modified directly by alcohol (Israel and Mardones, 1971), caffeine (Gilbert, 1976) diazepam (Warburton, 1975) and THC (Harris, 1978). In contrast, amphetamine which only acts on the dopamine and noradrenalin systems, is relatively specific (Lemberger and Rubin, 1976). From the balance of evidence available, smoking doses of nicotine only act directly on some of the acetylcholine systems in the body (the so called "nicotinic" pathways). Nicotine's molecular structure is similar enough to the acetylcholine molecule to mimic it and so produce normal changes in these pathways. This specificity of action decreases the likelihood that a drug will produce unwanted "side effects". This aspect will be discussed in more detail in the next section on toxicity.

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5. Toxicity

Almost all substances have toxic effects if taken in large doses for a sufficiently long period of time. In this section we will consider the acute, unwanted effects of the reference compounds and the chronic consequences of normally-used doses taken over a long period of time.

Although amphetamine can improve performance in laboratory tests there is evidence that the drug also distorts judgement so that the subject believes that the improvement is greater than it is. As well as distorting judgement, amphetamine acts as a sleep and appetite suppressant, and chronic use of the drug invariably leads to loss of weight due to reduced food intake. Repeated use of the drug results in tolerance so that higher and higher doses are needed to obtain the stimulant effects. Frequent small doses of amphetamines produce psychotic episodes in normal subjects (Kornetsky, 1976) and repeated use of high doses result in severe psychosis. Obviously amphetamine use is fraught with risks.

Caffeine is a much less harmful stimulant than amphetamine but is not without toxic effects. Gilbert (1976) reviewed the literature and concluded that there is considerable risk to the health of an average adult from the consumption of over 600 mg of caffeine a day (about eight cups of coffee). Such an adult will be more likely to experience headaches, insomnia, anxiety and depression on waking. Repeated use increases the likelihood of myocardial infarction, stomach ulcers, duodenal ulcers, and carcinoma of the kidneys and urinary tract. Recently it has been implicated with pancreatic cancer (MacMahon et al, 1981). Clearly, caffeine is not an entirely harmless compound although it is a much safer, but less potent, psychostimulant than amphetamine.

In view of alcohol's non-specific biochemical action it is not surprising that moderate doses of alcohol have a variety of acute unwanted consequences. It has a general, non-selective effect on all neural systems which lead to impairment of all types of performance eg thought, memory, concentration, fine movement, and motor control. As a consequence, anxiolytic doses are incompatible with most types of work. Moderate drinking probably cause very little chronic toxicity in terms of psychological and physiological functioning but repeated use of the drug

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results in larger and larger doses being required for anti-anxiety effects. Long term use of larger amounts leads to deterioration of the brain, liver and other organs (Wallgren and Barry, 1971).

The most common side effects of diazepam is drowsiness and impairment of concentration. These acute toxic effects are small but not insignificant in a fit, unfatigued person who has taken no alcohol, but are hazardous in a tired person or someone who has taken even a small amount of alcohol. It should also be remembered that the drug persists in the body for days and so the alcohol interaction could occur long after taking a dose. The evidence for chronic toxicity with diazepam is small and, although some tolerance develops, there is not the dramatic escalation of doses that can occur with alcohol (Marks, 1978). From the point of view of acute and chronic toxicity diazepam is a much safer anxiolytic than alcohol.

Alcohol use is often compared unfavourably with marijuana use, but the problem with this toxicity comparison is that we know so little about Δ^9-tetrahydrocannabinol (THC) and its active metabolites. Performance testing has revealed that cognitive ability and reaction time are impaired and, not surprisingly, driving skills (see review in Warburton, 1975 and Kornetsky, 1976). There is no evidence that repeated casual use has adverse consequences but an amotivational syndrome after frequent use of marijuana has been reported (Warburton, 1975; Kornetsky, 1976).

A typical list of the toxic effects of nicotine includes sweating, tremor, nausea, vomiting, abdominal pain, diarrhoea, palpitation, fatigue and headache (Cohen and Roe, 1981) but of these symptoms only tremor occurs in experienced smokers which suggests that either tolerance to these effects has occurred or the smoker titrates his dose to avoid the unwanted adverse effects. There is no evidence of intellectual impairment during use and, on the contrary, nicotine improves psychological performance (see Section IV D). This benign action seems to be due to the similarity between nicotine and acetylcholine, so that nicotine acts in a natural way on neurones and only produces changes in the brain which occur normally in states of alertness. As a consequence of its similarity to acetylcholine, tolerance to its action on electrocortical arousal does not occur (Murphree, 1979). This lack of tolerance is not surprising because neurones cannot become tolerant to their own chemicals otherwise they would cease to

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function. Without tolerance to the desired effects, smokers do not have to keep on increasing the dose to achieve the desired amounts of sedation or stimulation. Evidence for chronic toxicity due to nicotine alone, rather than cigarette smoke, is sparse and there is little convincing evidence of intellectual impairment even after a lifetime of use. Chronic nicotine use has sometimes been linked to gastrointestinal disturbance and cardiovascular disorders but no studies have controlled for caffeine and alcohol consumption which are associated with both sorts of disorder. Thus, nicotine, in smoking doses, has little known toxicity itself and the hazard to the smoker is in the other smoke constituents.

In summary, the ranking of compounds for toxicity, considering the doses which are in general use, would be alcohol (severe toxicity with potentially severe chronic toxicity), amphetamine (minor acute toxicity but severe chronic toxicity), marijuana (acute toxicity and perhaps minor chronic toxicity) caffeine (minor acute toxicity and moderate chronic toxicity), diazepam (minor acute toxicity and little chronic toxicity), and nicotine (no acute toxicity in smoking doses and little known chronic toxicity).

6. Abuse Potential

Use of any substance can only be evaluated with respect to the situation of use, the manner of use as well as the consequences of use (Balter, 1974). Normal use can be defined as consumption for an innocuous or constructive purpose in moderate amounts and in the appropriate context in terms of place and culture. Abuse focuses on adverse consequences of use in terms of physiological or pyschological effects. The consequences of abuse are organ damage and impairment of social and personal functioning. Indirectly, abuse refers to the manner of use by the person (pattern and amount taken). The problem of abuse is in the person's interaction with the compound and is not a fault of the compound itself. However, some substances are more likely to lead to abuse than others and this aspect is referred to as abuse potential. The abuse potential of a substance can be defined in terms of its intrinsic attractiveness (Balter, 1974), the number of users (Balter, 1974) and the number of users who become abusers of the substances (Balter, 1974).

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7. Intrinsic Attractiveness

Attractiveness refers to the extent to which most users find the immediate effect of a substance intrinsically pleasing. Intrinsic attractiveness is independent of cultural factors and can be assessed from laboratory studies with animals. In the laboratory, animals learn to lever press in order to self-administer some drugs and intrinsic attractiveness is assessed from the ease of learning and the regularity of pressing. While animals will rapidly self-administer amphetamines showing the high intrinsic attractiveness of this compound, animals self-administer alcohol and THC to a much lesser extent showing that these compounds have less intrinsic attractiveness. There is no evidence that animals will self administer diazepam or caffeine at all, indicating negligible intrinsic attractiveness. Attempts to train animals to self inject nicotine or "to smoke" have been rather unsuccessful which suggests very low intrinsic attractiveness (Kumar, 1979).

These laboratory studies fit with human comparisons of the compounds which indicate that intravenous amphetamine produces pleasure like a "pharmacogenic" orgasm, alcohol and THC produce moderate euphoria, while caffeine produces stimulation but no euphoria and diazepam is pleasurably relaxing but does not produce euphoria. Nicotine can be either mildly stimulating or pleasurably relaxing depending on the situation, but is not a euphoriant. The production of euphoria seems to be essential for high intrinsic attractiveness and for strong habit formation.

The strength of habit formation for non-durable commodities has been estimated by economists by time series analyses of demand (see Houthakker and Taylor, 1966). In their equations they include a parameters for the psychological "stock" of consumption habits because for some commodities, demand does not adjust to changes in prices or income. Current consumption is positively influenced by use of the commodity in the more or less recent past indicating some degree of habit formation. If a smoker has built up a psychological "stock" of smoking habits, then the number of cigarettes that have been smoked in the past will influence current consumption. If we consider the same population (eg United States 1929-1960, before any of the health campaigns), then we can compare the psychological "stock" for

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tobacco consumption with that for alcohol consumption by using the estimates for this parameter in the demand equations. These estimates show that tobacco use was subject to some habit formation (positive parameter value of 0.1743) but it was much smaller than psychological "stock" for alcohol consumption (parameter value of 1.0869). This conclusion would be consistent with the information on relative intrinsic attractiveness of alcohol and nicotine.

In summary, amphetamine produces a very pleasing effect on most people. Alcohol and THC are moderately attractive while caffeine, nicotine and diazepam have little intrinsic attractiveness.

8. Percentage of Abusers

An abuser is a person who is consuming a drug in sufficient quantities to produce damage to health. A comparison of the number of users and abusers is difficult because nicotine, caffeine and alcohol are readily available while amphetamine and diazepam are controlled and marijuana (THC) is illegal. However, the pattern of available evidence is consistent with the data on intrinsic attractiveness. When amphetamines were freely available on prescription in Britain, 10% of the population of Newcastle were receiving amphetamine prescriptions and 20% of the users were abusing the compound (Kiloh and Brandon, 1962). Alcohol and caffeine are socially acceptable substances which are consumed by over 95% of the population in most Western cultures and of these about 5-7% abuse alcohol (Kissin, 1972) and about 3% are caffeine abusers (Gilbert, 1976). It is estimated that 5-7% of THC users are abusers (Kissin, 1973). Abusers of diazepam are rare and current estimates would place the percentage at less than 1% (Marks, 1978). Strictly speaking, the number of abusers of nicotine is zero since few individuals take pure nicotine and nicotine itself is not known to contribute to the smoke-related disorders (Cohen and Roe, 1981).

Abuse potential has also been defined in terms of difficulty of stopping use. Of the reference substances, comparable data are only available on alcohol and smoking. Hunt and Bespalec (1974) compared the relapse rates for alcoholics and smokers with heroin (an agent with very high intrinsic attractiveness) and found that the relapse curves were very

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similar. This similarity has been used as evidence for the strong abuse potential of nicotine and for a common mechanism underlying use of all these substances. However, as Jaffe and Jarvik (1978) point out, while one may wonder what drives a heroin abuser to relapse in the face of the social disapproval, the physical hazards and legal risks of heroin use, it is surprising that relapse among ex-smokers is not universal given the multiple motives for smoking and the fact that a heavy smoker will experience the beneficial effects of stimulation or sedation from nicotine hundreds of times a year.

In summary, the overall rankings for abuse potential of the substances in terms of intrinsic attractiveness and number of users is amphetamine, alcohol, marijuana, caffeine with diazepam and nicotine having virtually zero abuse potential.

9. Conclusions

Nicotine, as used by the smoker, is a low risk substance in terms of acute and chronic toxicity and the smoke-related diseases can only be due to the other smoke constituents. Its rapid uptake into the brain allows smokers to control their psychological state at will so that they can obtain either stimulation or sedation to help them to cope with situations. Nicotine's specific action on the brain produces neural changes which are within normal limits and so nicotine acts in a normal way to produce stimulation and sedation. Nicotine is not like other so called "addictive" substances and has low abuse potential. The smoking habit is so strong because of the ability of nicotine to provide smokers with exquisite personal control over their psychological functioning. If future research could reduce those smoke constituents that produce toxicity then people, who need the benefits of nicotine, could obtain these without risk. Certainly no comparable, lower risk compounds are available at the moment.

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VI. CONCLUDING COMMENTS

Tobacco has been used in the Americas for three thousand years and its use has spread to nearly every culture in the world in the last five hundred years. Cigarette smokers puff a rod of burning tobacco and the majority of them inhale the smoke. As a consequence of smoke intake, a number of smoke constituents are absorbed and nicotine is the most active pharmacological ingredient of these compounds. Nicotine is absorbed very efficiently, enters the brain very quickly and a smoking dose is metabolised in 40 minutes which allows for brief duration of action. Smokers are sensitive to their plasma nicotine levels and they can control their intake of nicotine because of the rapidity of uptake and their perception of the moment to moment changes of nicotine level in their brain. Not only do smokers control nicotine by varying their cigarette consumption, but they control the strength of puffing to modify smoke generation, the amount of smoke retained for inhaling, and the degree of smoke inhalation for nicotine absorption. This control is more than avoidance of high toxic doses of nicotine but is an attempt to titrate for a specific nicotine dose by smoking high nicotine products less intensely and smoking low nicotine cigarettes more intensely.

The smoker's aim in titrating is obtaining an optimal dose of nicotine which will act on the body and satisfy some need. Experiments have revealed that nicotine has many actions on the body but only a very small proportion of these studies have used nicotine doses which are equivalent to smoking doses. The most consistent effect with smoking doses of nicotine is stimulation of a subset of the cholinergic neurones (ie the "nicotinic" pathways), including the autonomic nervous system and the ascending cholinergic pathways to the cortex and limbic system. The reason for this specificity of action is the similarity of the nicotine and acetylcholine molecules.

The outcome of these actions is an increase in blood levels of catecholamines and glucocorticoids and greater amounts of cortical desynchronization. All these changes are within the normal limits of the average person. Smokers believe that cigarettes aleviate mental and muscular fatigue to some extent and these effects can be attributed,

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in part, to the mobilization of energy reserves by the catecholamines and glucocorticoids. Smokers also claim that smoking helps them think and concentrate. Experimental studies with smokers have supported this claim and shown that nicotine can produce absolute enhancements in performance as well as preventing the performance decrements usually found during sustained performance. Enhanced performance of the same magnitude was found when nicotine tablets were given to non-smokers. A third important effect of nicotine is its sedative action which has been supported by questionnaire and experimental studies of smoking.

Measures of smoking behaviour during performance and while subjects are under stress show that smokers vary their nicotine intake according to the situation. In this way they obtain the required nicotine dose for stimulation or sedation depending on the situation. The rapid absorption and rapid metabolism make this substance suitable for hour-by-hour self-medication because of the personal control that can be exercised. In this respect nicotine is superior to other compounds for medication.

Nicotine taken in smoking doses seems to be relatively safe for healthy adults to use. On the evidence available at the moment it acts specifically on only a subset of the acetylcholine pathways in the body producing few side effects and none of these interfere with the normal functioning of body and mind. Even after a lifetime of use, the chronic toxicity of nicotine appears to be low. Thus nicotine stands in marked contrast to the deleterious short term and long term consequences of the socially acceptable substance, ethyl alcohol.

A number of important implications follow from these facts about nicotine. If smokers derive beneficial effects from nicotine and cigarettes are the most effective method of administering nicotine then cigarettes should be designed to deliver nicotine with minimum risk from smoke-related diseases. In my view the current trend of continuing to reduce nicotine as well as tar and carbon monoxide is not having the expected health benefits because smokers are compensating by puffing harder and inhaling more smoke. It has been argued that because compensation can only be partial with low delivery brands, intake of tar and carbon monoxide is still less than when high delivery brands were smoked and so

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these products have less risk (Rawbone, 1979). This argument would be true if cigarette consumption did not increase. However a recent paper (Wald et al, 1981) reported that over the 25 year period 1949-1974 sales-weighted average nicotine monotonically decreased. Tobacco industry figures confirm that sales-weighted nicotine monotonically decreased until 1975 from 1965, when its data were first available (RSL, 1981). In 1949, sales-weighted average nicotine was 74% higher than in 1974, representing a nicotine difference of 3.0% per annum. Over these 25 years, cigarette consumption for male smokers (RSL, 1981) increased by 50%, an average annual change of 2.0%, reflecting two-thirds compensation by consumption alone. The increase in consumption for women was even greater, as social influences contributed - it became more fashionable for females to smoke over this period. Since the mid-'70s, consumption has been affected by economic factors such as the recession and stringent tobacco taxation which make strong conclusions difficult. Nevertheless, it is intriguing that the recent downturn in consumption has coincided with a slight increase in average nicotine yield (Wald et al, 1981).

In conventional cigarette design, tar and nicotine tend to co-vary, ie low tar also entails low nicotine. Most popular cigarettes have a nicotine yield, as measured by a smoking machine, of at least 1.3 mg per cigarette, the best-selling brand having a nicotine yield of 1.6 mg per cigarette (DHSS, 1981). Low tar cigarettes, however, have an average nicotine yield of only 0.7 mg per cigarette (about half popular requirement). Perhaps it is no coincidence that these low tar - low nicotine cigarettes have now, for a number of years, hovered around 15% market share - which is the same as the estimated proportion of "social smokers" (McKennell and Thomas, 1967), ie that minority group who, according to motivational researchers, smoke cigarettes for non-nicotine reasons (McKennell, 1973). For the majority of smokers, however, such low strength cigarettes are not satisfying: compensatory mechanisms became inadequate, as the effort necessary to generate required levels of nicotine is too great. A more effective approach for minimising risk and maximising benefit would be a product with medium nicotine delivery but a reduction of most other smoke components. For this concept to be acceptable, it is obviously crucial that such a cigarette also conveys sufficient flavour appeal. The Independent Scientific Committee already recognises the importance of flavour as a prerequisite for smoker satisfaction (Second Report, 1978). It is therefore essential that the product would not need to be smoked

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more intensively, or require more smoke to be inhaled, in order to satisfy taste, or to delivery the optimal amount of nicotine to the smoker. However, optimal levels of nicotine are different for different sorts of smokers. It seems to depend on such determinants as personality, sex, and average daily consumption. Thus specific types of products could be required to delivery the optimal nicotine levels for differing smoker groups.

The tobacco industry has methods for modifying smoke delivery in order to partially dissociate nicotine from tar. Some of the more drastic smoke reduction procedures change the chemical nature of the smoke (Guerin, 1980) and the toxicological implication of these shifts is unknown. Russell (1979) has briefly reported some tests of reduced tar, medium nicotine cigarettes but his comments imply that they were less acceptable than conventional products. Thus the manipulations of smoke delivery, that have been attempted so far, are very unsatisfactory, not only because they may leave harmful smoke compounds but because they remove important flavours. Clearly, future progress must be in the direction of reduction of specific smoke constituents to reduce risk but maintain flavour.

Unfortunately, we have only a limited amount of toxicological information on a few of the 4000 identified compounds in tobacco and tobacco smoke on which to base a selective reduction strategy. It is said that tobacco smoke is a relatively mild carcinogen (Tso, 1980) which means either that the hazardous compound or compounds are only weak carcinogens or the toxic compound is present in very small quantities. In the latter case the task of identification of the constituents to be reduced will be formidable.

Problems may also arise with the identification of key flavours because taste sensitivity is not uniform across the flavour spectrum. This non-uniformity means that some smoke constituents which are present in large amounts may contribute very little to smoke flavour while a trace component may be essential for a balanced sensory impact. Conceivably chemicals that are essential flavour components could also be hazardous (Second Report, 1978). In this case, non-toxic, flavour additives will have to be substituted for the desired flavour and to

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fortify the other flavours in order to preserve the characteristic full flavour impact for the smoker.

It is clear that the way to a less hazardous cigarette is not an easy one. However, the development of a medium nicotine cigarette, possibly with reduction of some smoke components, suitably enhanced with flavour, could well represent an important milestone along this path. The end of the road could not only be a safer cigarette but also a more satisfying one. Nicotine has much to commend it.

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